APPLICANT: Stanley T. Crooke DOCKET NO: ISIS-5027

SERIAL NO: 10/078,949

AMENDMENTS TO THE CLAIMS: This listing of claims replaces all prior versions and listings of claims in the instant patent application.

1-164. (Canceled)

- 165. (Currently amended) A method of activating a double-stranded RNA nuclease, comprising:
- (i) contacting the nuclease with a double-stranded nucleic acid oligomeric compound comprising a first oligonucleotide and a second oligonucleotide, wherein:

at least one of said first and said second oligonucleotides comprises at least four consecutive 2'-hydroxyl ribonucleosides and at least one chemical modification; said first and said second oligonucleotides are hybridized to each other; and said first and said second oligonucleotides are not covalently linked to each other; and wherein

said first and said second oligonucleotides are each independently from 15 to 25 nucleoside subunits in length; and

- (ii) detecting activation of said double-stranded RNA nuclease.
- 166. (Canceled)
- 167. (Previously presented) The method of claim 165, wherein the at least one chemical modification increases resistance of said oligonucleotide to single-stranded nucleases and/or increases the affinity of said oligonucleotide to the other oligonucleotide.
- 168. (Previously presented) The method of claim 167, wherein at least one modification is 2'-methoxy.
- 169. (Previously presented) The method of claim 167, wherein at least one modification is 2'-fluoro.
- 170. (Previously presented) The method of claim 167, wherein at least one modification is 2'-O-methoxyethyl.
- 171. (Previously presented) The method of claim 167, wherein at least one modification is a phosphorothioate internucleoside linkage.
- 172. (Previously presented) The method of claim 165, wherein said first oligonucleotide and said second oligonucleotide each have at least four consecutive 2'-hydroxyl ribonucleosides.

- 173. (Previously presented) The method of claim 172, wherein the 2'-hydroxyl residues of said first and said second oligonucleotides have phosphodiester linkages.
- 174. (Previously presented) The method of claim 172, wherein the 2'-hydroxyl residues of said first and said second oligonucleotides have phosphorothioate linkages.
- 175. (Previously presented) The method of claim 172, wherein the 2'-hydroxyl residues of said first oligonucleotide have phosphodiester linkages and the 2'-hydroxyl residues of said second oligonucleotide have phosphorothioate linkages.
- 176. (Previously presented) The method of claim 172 or claim 175, wherein said first and said second oligonucleotides further comprise flanking residues 5' and 3' of the 2'-hydroxyl ribonucleosides, wherein said flanking residues have phosphorothioate linkages.
- 177. (Previously presented) The method of claim 176, wherein said flanking residues of at least one of said first and said second oligonucleotides further comprises 2'-methoxynucleosides.
- 178. (Previously presented) The method of claim 176, wherein said flanking residues of each of said first and said second oligonucleotides further comprise 2'-methoxynucleosides.
- 179. (Previously presented) The method of claim 165, wherein at least one of said first and said second oligonucleotides comprises at least eight consecutive 2'-hydroxyl ribonucleosides.
- 180. (Previously presented) The method of claim 179, wherein said first oligonucleotide and said second oligonucleotide each comprise at least eight consecutive 2'-hydroxyl ribonucleotides.
- 181. (Previously presented) The method of claim 165, wherein each of said first and said second oligonucleotides are about 17 to about 20 nucleoside subunits in length.
- 182. (Previously presented) The method of claim 181, wherein each of said first and said second oligonucleotides are 17 subunits in length.
- 183. (Previously presented) The method of claim 181, wherein each of said first and said second oligonucleotides are 20 subunits in length.

184-201. (Canceled)

202. (Currently amended) A method of activating a double-stranded RNA nuclease comprising contacting the <u>double-stranded RNA</u> nuclease with a double-stranded nucleic acid <u>oligomeric compound</u> comprising a first oligonucleotide and a second oligonucleotide, wherein:

said first and said second oligonucleotides are <u>each</u> independently 15 to 25 nucleoside subunits in length;

said first and said second oligonucleotides are hybridized to each other; said first and said second oligonucleotides are not covalently linked to each other; and

at least one of said first and said second oligonucleotides comprises at least four consecutive 2'-hydroxyl ribonucleosides and at least one chemical modification.

- 203. (Previously presented) The method of claim 202 wherein at least one chemical modification increases resistance to single-stranded nucleases.
- 204. (Previously presented) The method of claim 202 wherein at least one chemical modification increases affinity of said first oligonucleotide to said second oligonucleotide.
- 205. (Previously presented) The method of claim 202 wherein at least one chemical modification is a modified internucleoside linkage, a modified sugar moiety or a modified nucleobase.
- 206. (Previously presented) The method of claim 202 wherein at least one chemical modification is a phosphorothioate internucleoside linkage.
- 207. (Previously presented) The method of claim 202 wherein at least one chemical modification is a 2'-substituted sugar modification.
- 208. (Previously presented) The method of claim 202 wherein at least one chemical modification is a 2'-alkoxy sugar modification.
- 209. (Previously presented) The method of claim 202 wherein at least one chemical modification is a 2'-methoxy sugar modification.
- 210. (Previously presented) The method of claim 202 wherein at least one chemical modification is a 2'-fluoro sugar modification.
- 211. (Previously presented) The method of claim 202 wherein at least one chemical modification is a 2'-O-methoxyethyl sugar modification.

- 212. (Previously presented) The method of claim 202 wherein each of said first and said second oligonucleotides comprises at least four consecutive 2'-hydroxyl ribonucleosides.
- 213. (Previously presented) The method of claim 202 wherein each of said first and said second oligonucleotides comprises at least one chemical modification.
- 214. (Previously presented) The method of claim 202 wherein each of said first and said second oligonucleotides comprises at least four consecutive 2'-hydroxyl ribonucleosides and at least one chemical modification.
- 215. (Previously presented) The method of claim 202 wherein said first oligonucleotide and said second oligonucleotide comprise at least 17 contiguous nucleotides which are 100% complementary to each other.
- 216. (Previously presented) The method of claim 202 wherein said first oligonucleotide is 100% complementary to said second oligonucleotide.
- 217. (Previously presented) The method of claim 202 wherein said first oligonucleotide and said second oligonucleotide are independently 17 to 20 nucleoside subunits in length.
- 218. (Previously presented) The method of claim 202 further comprising detecting activation of said double-stranded RNA nuclease.
- 219. (Currently amended) A method of activating a double-stranded RNA nuclease comprising contacting the <u>double-stranded RNA</u> nuclease with a double-stranded nucleic acid <u>oligomeric compound</u> comprising a first oligonucleotide and a second oligonucleotide, wherein:

said first and said second oligonucleotides are <u>each</u> independently 15 to 25 nucleoside subunits in length;

said first and said second oligonucleotides are hybridized to each other; said first and said second oligonucleotides are not covalently linked to each other; and

at least one of said first and said second oligonucleotides comprises: a plurality of nucleoside subunits with 2'-hydroxyl pentofuranosyl sugar moieties; and at least one chemical modification.

220. (Previously presented) The method of claim 219 wherein at least one chemical

modification increases resistance to single-stranded nucleases.

- 221. (Previously presented) The method of claim 219 wherein at least one chemical modification increases affinity of said first oligonucleotide to said second oligonucleotide.
- 222. (Previously presented) The method of claim 219 wherein at least one chemical modification is a modified internucleoside linkage, a modified sugar moiety or a modified nucleobase.
- 223. (Previously presented) The method of claim 219 wherein at least one chemical modification is a phosphorothioate internucleoside linkage.
- 224. (Previously presented) The method of claim 219 wherein at least one chemical modification is a 2'-substituted sugar modification.
- 225. (Previously presented) The method of claim 219 wherein at least one chemical modification is a 2'-alkoxy sugar modification.
- 226. (Previously presented) The method of claim 219 wherein at least one chemical modification is a 2'-methoxy sugar modification.
- 227. (Previously presented) The method of claim 219 wherein at least one chemical modification is a 2'-fluoro sugar modification.
- 228. (Previously presented) The method of claim 219 wherein at least one chemical modification is a 2'-O-methoxyethyl sugar modification.
- 229. (Previously presented) The method of claim 219 wherein each of said first and said second oligonucleotides comprises a plurality of nucleoside subunits with 2'-hydroxyl pentofuranosyl sugar moieties.
- 230. (Previously presented) The method of claim 219 wherein each of said first and said second oligonucleotides comprises at least one chemical modification.
- 231. (Previously presented) The method of claim 219 wherein each of said first and said second oligonucleotides comprises a plurality of nucleoside subunits with 2'-hydroxyl pentofuranosyl sugar moieties and at least one chemical modification.
- 232. (Previously presented) The method of claim 219 wherein said first oligonucleotide and said second oligonucleotide comprise at least 17 contiguous nucleotides which are 100% complementary to each other.

- 233. (Previously presented) The method of claim 219 wherein said first oligonucleotide is 100% complementary to said second oligonucleotide.
- 234. (Previously presented) The method of claim 219 wherein said first oligonucleotide and said second oligonucleotide are independently 17 to 20 nucleoside subunits in length.
- 235. (Previously presented) The method of claim 219 further comprising detecting activation of said double-stranded RNA nuclease.
- 236. (Currently amended) A method of activating a double-stranded RNA nuclease comprising contacting the <u>double-stranded RNA</u> nuclease with a double-stranded nucleic acid <u>oligomeric compound</u> comprising a first oligonucleotide and a second oligonucleotide, wherein:

said first and said second oligonucleotides are hybridized to each other; said first and said second oligonucleotides are not covalently linked to each other; and

said first and said second oligonucleotides are each independently from 15 to 25 nucleoside subunits in length; and

each of said first and said second oligonucleotides comprises at least four consecutive 2'-hydroxyl ribonucleosides and at least one chemical modification.

- 237. (Previously presented) The method of claim 236 wherein at least one chemical modification increases resistance to single-stranded nucleases.
- 238. (Previously presented) The method of claim 236 wherein at least one chemical modification increases affinity of said first oligonucleotide to said second oligonucleotide.
- 239. (Previously presented) The method of claim 236 wherein at least one chemical modification is a modified internucleoside linkage, a modified sugar moiety or a modified nucleobase.
- 240. (Previously presented) The method of claim 236 wherein at least one chemical modification is a phosphorothioate internucleoside linkage.
- 241. (Previously presented) The method of claim 236 wherein at least one chemical modification is a 2'-substituted sugar modification.
 - 242. (Previously presented) The method of claim 236 wherein at least one chemical

modification is a 2'-alkoxy sugar modification.

- 243. (Previously presented) The method of claim 236 wherein at least one chemical modification is a 2'-methoxy sugar modification.
- 244. (Previously presented) The method of claim 236 wherein at least one chemical modification is a 2'-fluoro sugar modification.
- 245. (Previously presented) The method of claim 236 wherein at least one chemical modification is a 2'-O-methoxyethyl sugar modification.
- 246. (Previously presented) The method of claim 236 further comprising detecting activation of said double-stranded RNA nuclease.
- 247. (Currently amended) A method of activating a double-stranded RNA nuclease comprising contacting the <u>double-stranded RNA</u> nuclease with a double-stranded nucleic acid <u>oligomeric compound</u> comprising a first oligonucleotide and a second oligonucleotide, wherein:

said first and said second oligonucleotides are hybridized to each other; said first and said second oligonucleotides are not covalently linked to each other;

said first and said second oligonucleotides are 100% complementary to each other; and

at least one of said first and said second oligonucleotides comprises at least four consecutive 2'-hydroxyl ribonucleosides and at least one chemical modification.

- 248. (Previously presented) The method of claim 247 wherein at least one chemical modification increases resistance to single-stranded nucleases.
- 249. (Previously presented) The method of claim 247 wherein at least one chemical modification increases affinity of said first oligonucleotide to said second oligonucleotide.
- 250. (Previously presented) The method of claim 247 wherein at least one chemical modification is a modified internucleoside linkage, a modified sugar moiety or a modified nucleobase.
- 251. (Previously presented) The method of claim 247 wherein at least one chemical modification is a phosphorothioate internucleoside linkage.
 - 252. (Previously presented) The method of claim 247 wherein at least one chemical

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modification is a 2'-substituted sugar modification.

253. (Previously presented) The method of claim 247 wherein at least one chemical modification is a 2'-alkoxy sugar modification.

- 254. (Previously presented) The method of claim 247 wherein at least one chemical modification is a 2'-methoxy sugar modification.
- 255. (Previously presented) The method of claim 247 wherein at least one chemical modification is a 2'-fluoro sugar modification.
- 256. (Previously presented) The method of claim 247 wherein at least one chemical modification is a 2'-O-methoxyethyl sugar modification.
- 257. (Previously presented) The method of claim 247 further comprising detecting activation of said double-stranded RNA nuclease.
- 258. (Previously presented) The method of claim 219, wherein the double-stranded RNA nuclease is not in a cell.